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2. Patent application number *(The Patent Office will fill in this part)*
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*
   K.U.Leuven R&D - Groot Begijnhof - Benedenstraat 59 - 3000 Leuven 7665649001
   Represented by Prof. dr. ir. K. Debackere, Managing Director and Hans Claes, Director

   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention
   Insulin related methods or preparations for suppressing states of "Critical Illness Polyneuropathy"

5. Name of your agent *(if you have one)*

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   K.U.Leuven R&D
   Care Off:
   Dominique Newman
   Quartz Capital Limited
   3 St. James's Square 7816093001
   London SW1Y 4JU

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Number of earlier application	Date of filing *(day / month / year)*

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	1
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Any other documents *(please specify)*	1 fax cover sheet 1 fee sheet with request for fax back service

11. I/We request the grant of a patent on the basis of this application.

Hans Claes Director — Prof. dr. ir. K. Debackere Managing Director — Signature — Date 05/05/2000

12. Name and daytime telephone number of person to contact in the United Kingdom: Dominique Newman, tel. 0171 766 2900 or 0207 766 2900

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INSULIN RELATED METHODS OR PREPARATIONS FOR SUPPRESSING STATES OF 'CRITICAL ILLNESS POLYNEUROPATHY'

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TECHNOLOGICAL BACKGROUND

A specific type of polyneuropathy develops in patients that are treated within an intensive care unit (ICU) for several days to weeks and this for a variety of primary injuries or illnesses. This polyneuropathy, known as "Critical Illness Polyneuropathy" (CIPNP) occurs in 70% of patients who have the systemic inflammatory response syndrome (SIRS) (Zochodne DW et al. 1987 Polyneuropathy associated with critical illness : a complication of sepsis and multiple organ failure. Brain, 110: 819-842); (Leijten FSS & De Weerdt AW 1994 Critical illness polyneuropathy: a review of the literature, definition and pathophysiology. Clinical Neurology and Neurosurgery, 96: 10-19). However, clinical signs are often absent and it remains an occult problem in many ICUs worldwide. Nonetheless, it is an important clinical entity as it a frequent cause of difficulty to wean patients from the ventilator and it leads to problems with rehabilitation after the acute illness has been treated and cured.

When CIPNP is severe enough, it causes limb weakness and reduced tendon reflexes. Sensory impairment follows but is difficult to test in ICU patients. Electrophysiological examination (EMG) is necessary to establish the diagnosis (Bolton CF. 1999 Acute Weakness. In: Oxford Textbook of Critical Care; Eds. Webb AR, Shapiro MJ, Singer M, Suter PM; Oxford Medical Publications, Oxford UK; pp. 490-495). This examination will reveal a primary axonal degeneration of first motor and then sensory fibers. Phrenic nerves are often involved. Acute and

chronic denervation has been confirmed in muscle biopsies of this condition. If the underlying condition (sepsis or SIRS) can be successfully treated, recovery from the CIPNP can be expected. This will occur in a matter of weeks in mild cases and in months in more severe cases. In other words, the presence of CIPNP can delay the weaning and rehabilitation for weeks or months.

The pathophysiology of this type of neuropathy remains unknown (Bolton CF 1996 Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations. Crit Care Med. 24: 1408-1416). It has been speculated to be directly related to sepsis and its mediators. Indeed, cytokines released in sepsis have histamine-like properties which may increase microvascular permeability. The resulting endoneural edema could induce hypoxia, resulting in severe energy deficits and hereby primary axonal degeneration. Alternatively, it has been suggested that cytokines may have a direct cytotoxic effect on the neurons. Contributing factors to disturbed microcirculation are the use of neuromuscular blocking agents and steroids. Moreover, a role for aminoglucosides in inducing toxicity and CIPNP has been suggested. However, there is still no statistical proof for any of these mechanisms in being a true causal factor in the pathogenesis of CIPNP.

Although polyneuropathy of critical illness was first described in 1985 by three different investigators, one Canadian, one American, and one French, to date there is no effective treatment to prevent or stop Critical Illness Polyneuropathy.

SUMMARY OF THE INVENTION

This invention was based on the discovery that CIPNP can be prevented, to a certain extent, by strictly controlling glucose metabolism during critical illness by applying intensive insulin treatment with clamping of blood glucose levels within the normal range (80-110 mg/dL). To date the current standard of practice of care was that within the settings of good clinical ICU practice, blood glucose levels are allowed to increase as high as to 250 mg/dL or there above. The reason for this permissive attitude is the thought that high levels of blood glucose are part of the adaptive stress responses, and thus do not require treatment unless extremely elevated (Mizock BA. Am J Med 1995; 98: 75-84). Also, relative hypoglycaemia during stress is thought

to be potentially deleterious for the immune system and for healing (Mizock BA. Am J Med 1995; 98: 75-84)

This invention demonstrates that clamping of blood glucose levels within normal limits (80 to 110 mg/dL) in chronic ill patients can be used to significantly reduce the incidence of CIPNP and to lengthen the time free of CIPNP in patients that do develop this problem.

In the illustrative embodiment of present invention blood glucose levels were controlled by insulin treatment. However after this invention, it will be clear for the man skilled in the art that also active insulin derivatives and its physiologically tolerated salts can be used to obtain the same outcome.

Furthermore it will be clear for the man skilled in the art compounds of the group of biologically active substances having insulin releasing action can be used to treat Critical Illness Polyneuropathy or to manufacture a medicine to treat Critical Illness Polyneuropathy. Such compound with an activity of promoting the secretion of insulin were already well disclosed before the moment of this invention such as the Islets-Activating Proteins (Ui; Michio et al US5000953 March 19, 1991) and the glucagon-like peptides (Habener; Joel F. Newton Highlands, MA US5614492 March 25, 1997)

Furthermore it will be clear for the man skilled in the art compounds of the group of compounds that stimulate signal transduction mediated by an insulin receptor type tyrosine kinase in a cell can be used to treat or to manufacture a medicine to treat Critical Illness Polyneuropathy. It was well known before the date of this invention that insulin binding to the insulin receptor triggers a variety of metabolic and growth promoting effects. Metabolic effects include glucose transport, biosynthesis of glycogen and fats, inhibition of triglyceride breakdown, and growth promoting effects include DNA synthesis, cell division and differentiation. It is known that some of these biological effects of insulin can be mimicked by vanadium salts such as vanadates and pervanadates. However, this class of compounds appears to inhibit phosphotyrosine phosphatases generally, and are potentially toxic because they contain heavy metal (U.S. Pat. No. 5,155,031; Fantus et al., 1989, Biochem., 28:8864-

71; Swarup et al., 1982, Biochem. Biophys. Res. Commun. 107:1104-9). Moreover it had been already demonstrated (LAMMERS REINER et al 1999-01-19 US5861266 & WO9523217) that certain protein-tyrosine phosphatases (PTP's), in particular, RPTP.alpha. and RPTP.epsilon., specifically regulate the insulin receptor signalling pathway. Compounds that specifically modulate the activity of the controlling RPTP, thereby prolonging or enhancing signal transduction mediated by the insulin receptor can thus be used to treat Critical Illness Polyneuropathy or to manufacture a medicine to treat Critical Illness Polyneuropathy. Such compounds have low toxicity since they are specific for the PTPs associated with insulin receptor activity, and do not significantly affect the activity of other PTPs that are non-specific

DEFINITIONS

The term "systemic inflammatory response syndrome (SIRS)", as used herein refers to the uncontrolled disease process which ensues an initial insult and which gives rise to a multisystem disturbance secondary to inflammatory mediators released during shock.

The term "Sepsis", as used herein refers to "SIRS", as described above, which is particularly caused by an infectious insult leading to the initial shock phase.

The term "mediators of sepsis", as used herein refers to factors released by inflammatory cells, such as TNFs, interleukins, bradykinins etc.

The term "insulin receptor type tyrosine kinase", as used herein refers to a post-receptor signal transduction pathway involved in the insulin signaling.

The term "Endoneural edema", as used herein refers to swelling of the neuronal cells.

The term "phrenic nerves", as used herein refers to the left and right nervus phrenicus, innervating the diaphragm.

DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENT

The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appending claims. This invention is not limited to the particular methodology, protocols, delivery forms and reagents described as these may vary

Material and Methods

In a prospective clinical study, we tested the hypothesis that the incidence of CIPNP can be reduced by more strict metabolic using intensive insulin treatment from admission onward.

Between February 2 and April 25 2000, 400 patients were included in the study. They had been randomly allocated to one of two insulin (Actrapid HM NovoLet of Novo Nordisk) treatment schedules :

(1) insulin infusion started at a dose of 1U/h only when blood glucose is > 230 mg/dL (13 mmol/L) and titrated up (2 to 4 hourly controls of blood glucose levels) with increments of 0.5 to 1 U/h to keep blood glucose below this level [180-200 mg/dL (10.3-11.2 mmol/L)]. When blood glucose levels reach 180 mg/dL, insulin infusion is stopped.

(2) insulin infusion started when blood glucose is > 120 mg/dL (6.8 mmol/L) at a dose of 2 U/h and titrated up (2 to 4 hourly controls of blood glucose levels) with increments adequate to keep blood glucose levels normal and thus below this level [80-110 mg/dL (4.6-6.1 mmol/L)]. Maximal hourly insulin dose is set at 60 U per hour. When blood glucose levels reach 80 mg/dL, insulin infusion is tapered and eventually stopped until normal levels are again reached. During interruption of enteral tube feeding for determination of residual stomach content, insulin infusion is reduced proportionately to the reduction of caloric intake.

Concomitantly, patients were fed, on the admission day using a 20% glucose infusion and from day 2 onward by using a standardised feeding schedule consisting

of normal caloric intake (25-35 Calories/kgBW/24h) and balanced composition (20%-40% of the non-protein Calories as lipids & 1-2 g/kgBW/24h protein) of either total parenteral, combined parenteral/enteral or full enteral feeding, the route of administration of feeding depending on assessment of feasibility of early enteral feeding by the attending physician. All other treatments, including feeding regimens, were according to standing orders currently applied within the ICU.

Exclusion criteria were age <18y, pregnancy and not being intubated at admission.

When patients were still treated in the ICU after 7 days, a weekly EMG examination was performed to screen for the presence of CIPNP. The EMGs were always interpreted by the same expert in electrophysiology. In order to accurately assess ICU stay, which is often determined by other factors than the patient's condition -- e.g. bed availability on the wards -- "end of ICU stay" was defined as the day on which the attending physician considers the patient to be "ready for discharge".

The study protocol had been approved by the University of Leuven School of Medicine Ethical Review Board (ML1094 -- dd 26-10-99).

Results

83 patients ended up being treated on the ICU for at least one week and were screened by EMG for the presence of CIPNP. In the group randomised into the "intensive insulin schedule", 38 patients stayed for more than 7 days and in the group randomised into the "restrictive insulin schedule", 45 patients stayed more than 7 days. Fifteen out of 38 long-stay ICU patients in the intensive insulin group (or 39% of the long stayers) revealed a positive EMG for CIPNP at any time during the ICU stay versus 30 out of 45 in the restrictive insulin group (or 67%) (P=0.01 with Chi-square).

In the intensive insulin group, the mean±SD number of positive EMGs for CIPNP per patient was 0.9±1.8 (median of zero) versus 1.8±2.1 (median of 1) in the restrictive insulin group (P=0.015 with Mann-Whitney U test).

Long-stay patients in the intensive insulin group had a CIPNP-free time on the ICU of 2.1±1.8 weeks versus 1.1±1.2 weeks in the restrictive insulin group (P=0.004 with unpaired Student's t-test).

ICU-mortality was not detectably different between the two treatment groups (P=0.4).

CONCLUSIONS

This study revealed that strict metabolic control with intensive insulin treatment and clamping of blood glucose levels within normal limits significantly reduces the incidence of CIPNP and lengthens the time free of CIPNP in patients that do develop this problem. This is the first study to point to a preventive strategy for this frequently occurring and important problem in ICU patients. Since the presence of EMG-proven CIPNP has been shown to extend the need for ICU support and to prolong the time required for rehabilitation, this treatment will lead to a reduction in need for ICU support and to a shorter time for rehabilitation, which could reflect a major reduction in costs.

CLAIMS

What is claimed is:

1. Use of a pharmaceutically effective composition for use in the therapeutic treatment of a mammal having Critical Illness Polyneuropathy, comprising a pharmaceutically effective amount of a compound which is selected from a group of compounds comprising insulin, its active derivatives and the physiologically tolerated salts of these insulin derivatives or of a group of biologically active substances having insulin releasing action or of a group of compounds that stimulate signal transduction mediated by an insulin receptor type tyrosine kinase in a cell.

2. Use of a pharmaceutically effective composition for use in the prophylactic treatment of a mammal having Critical Illness Polyneuropathy, comprising a pharmaceutically effective amount of a compound which is selected from a group of compounds comprising insulin, its active derivatives and the physiologically tolerated salts of these insulin derivatives or of the group of biologically active substances having insulin releasing action or of the group of compounds that stimulate signal transduction mediated by an insulin receptor type tyrosine kinase in a cell.

3. Use of compounds of the group of compounds comprising insulin, its active derivatives and the physiologically tolerated salts of these insulin derivatives or of a group of biologically active substances having insulin releasing action or of a group of compounds that stimulate signal transduction mediated by an insulin receptor type tyrosine kinase in a cell for the manufacturing of a medicament for the treatment or prevention of Critical Illness Polyneuropathy

4. A method for the treatment of Critical Illness Polyneuropathy in mammals, wherein said critical ill individual receives an effective amount of a compound to keep the blood glucose levels between 80 and 110 mg/dL (4.6-6.1 mmol/L).

5. The method of claim 4 whereby said compound is selected from a group of compounds comprising insulin, its active derivatives and the physiologically tolerated salts of these insulin derivatives or of a group of biologically active substances having insulin releasing action or of a group of compounds that stimulate signal transduction mediated by an insulin receptor type tyrosine kinase in a cell

ABSTRACT

This invention relates to the pharmaceutically effective composition to treat or prevent Critical Illness Polyneuropathy. The composition comprises a pharmaceutically effective amount of a compound which is selected from a group of compounds comprising insulin, its active derivatives and the physiologically tolerated salts of these insulin derivatives or of a group of biologically active substances having insulin releasing action or of a group of compounds that stimulate signal transduction mediated by an insulin receptor type tyrosine kinase in a cell.